UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

Date: December 9, 2010

SUBJECT: **Pyroxasulfone** [KIH-485(TGAI)] **Title:** Trilateral Joint Review Project. Toxicology and Metabolism: Evaluation and Assessment of the Data Submitted

PC Code: 090099
Decision No.: 409018

Petition No.: 9F7560
Risk Assessment Type: NA
TXR No.: 0055216
MRID No.: See list below for multiple listing

DP Barcode: D365227, D376449, D371261
Registration No.: 63588-OR- Pyroxasulfone Technical
Regulatory Action: Registration
Case No.:
CAS No.: 447399-55-5
40 CFR: NA

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I. CONCLUSIONS

The toxicology data base for the new chemical global joint project (trilateral review with Australia and Canada) **Pyroxasulfone** [KIH-485(TGAI)] is attached in the monograph entitled: "**PYROXASULFONE** Active Substance: ANNEX IIA, SECTION 3, Point 5, MAMMALIAN

TOXICOLOGY, SUMMARIES and ASSESSMENT, (TIERII – DOCUMENT M-II)" and is attached in two files: File 1 and File 2.

This document contains the toxicity study summaries prepared by the submitter. The responsibility for the primary review of these studies was with the Health Effects Division (HED) of the USEPA. Risk Assessment Branch IV (RAB IV) reviewed the summaries in detail to verify the findings in the study reports. Adjustments (additions, deletions, corrections) were made where necessary. Secondary reviews of these studies were conducted by the Australian and Canadian global partners. Comments from the partners were considered by HED and incorporated into the final version of the study summaries.

HED has prepared its own reports on cancer classification (CARC report dated, 2010, HED Document TXR # 0055356) and selection of the reference doses.

This submitted data was considered in support of the Human Health Risk Assessment for proposed herbicidal uses on wheat, corn and soybeans.

II. ACTION REQUESTED

Risk Assessment Branch IV (RAB IV) was requested to review the toxicity data base for pyroxasulfone submitted in support of proposed tolerances for food uses and to work in conjunction with the global partners (Canada and Australia). PMRA of Canada and APVMA of Australia provided secondary review of the toxicity studies. As part of the secondary review, PMRA reviewed the positive neurotoxicity control studies in conjunction with the pyroxasulfone DNT and subchronic neurotoxicity studies. As a part of the overall review of pyroxasulfone, RABIV prepared documents for review of pyroxasulfone by HED's Carcinogenicity Assessment Review Committee (CARC report dated, 2010, HED Document TXR # 0055356) and Risk Assessment Review Committee (RARC meeting on October 6, 2010).

III. MRID Summary Table and location of study in the monograph.

The following tables list the study type, MRID and year of the study, the NOAEL and LOAEL or other result, study classification according to HED criteria and the page within the monograph where the study is located. Acute, subchronic, chronic, developmental, mutagenicity, general metabolism and neurotoxicity studies are listed. Studies with metabolites are also included. Studies in the reports are linked to the Table of Contents.

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
Absorption, distribution excretion and metabolism in mammals FILE 1				
870.7485/ General metabolism	47701728 (2008)	Acceptable/ Guideline (O)	4-23	

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
870.7485/ General metabolism	47701729 (2008)		23-39	
Acute Toxicity				
870.1100/ Acute oral toxicity	47701677	Defer to RD		Category III
870.1200/ Acute dermal toxicity	47701684	Defer to RD		Category III
870.1300/ Acute inhalation toxicity	47701685	Defer to RD		Category IV
870.2500/ Primary dermal irritation	47701686	Defer to RD		Category IV
870.2400/ Primary eye irritation	47701687	Defer to RD		Category IV
870.2600/ Skin sensitization	47701688	Defer to RD		-
Short-Term Toxicity				
870.3050/ 28-day feeding study in rats	47701689 (2003)	Acceptable/ Guideline	40-52	LOAEL = 500 pm hepatocyte and myocardial vacuolation; myocardial degeneration. NOAEL = 500 ppm
870.3050/ 28-day feeding study in rats	47889320 (2004)	Acceptable/ Nonguideline	439-446	CPK enzymes were not predictive markers of myocardial toxicity. **LOAEL** = 1000 ppm (75.4/84.4 mg/kg/day for M/F) based on myocardial degeneration/necrosis **NOAEL** = 100 ppm (7.3/8.3 mg/kg/day for M/F)
870.3100/ 90-day feeding study in Wistar rats	47701692 (2005)	Acceptable/ Guideline (Y)	52-66	LOAEL = 2500 ppm myocardial degeneration NOAEL = 500 ppm
870.3100/ 90-day feeding study in CD-1 rats	47701693 (2005)	Acceptable/ Guideline (Y)	66-80	LOAEL = 2500 ppm myocardial degeneration, centrilobular hepatocellular hypertrpophy, urinary bladder diffuse mucosal hyperplasia. NOAEL = 500 ppm
870.3100/ 90-day feeding in mice	47701694 (2005)	Acceptable/ Guideline (Y)	80-98	LOAEL = 5000 ppm, Target organs are heart, liver, kidney, NOAEL = 1000 ppm
870.3100/ 90-day feeding in mice	47701695 (2005)	Acceptable/ Guideline (Y)	98-105	LOAEL = 2500 ppm in females, chronic progressive nephropathy, tubular Regeneration. NOAEL = 250/2500 ppm in females /males
870.3150/ 90-day feeding in the dog	47701696 (2004)	Acceptable/ Guideline (Y)	106-113	LOAEL =10 mg/kg/day, muscle fiber and nerve degeneration NOAEL = 2 mg/kg/day
870.3150/ 90-day feeding in the dog	47701697 (2006)	Acceptable/ Guideline (Y)	113-123	LOAEL = 15 mg/kg/day, axonal/myelin degeneration in the sciatic nerve, inflammation of skeletal muscle, Impaired limb function, body and limb hypotonia, increase in serum CDK

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
				NOAEL : not established
870.4100b/ Chronic feeding in dogs	47701707 (2008)	Acceptable/ Guideline (Y)	123-134	LOAEL = 10 mg/kg/day, ataxia, tremors; clinical pathology: increased creatine kinase, aspartate aminotransferase; axonal/myelin degeneration of the sciatic nerve and spinal cord sections NOAEL = 2 mg/kg/day
870.3200/ 28 day dermal toxicity in rats	47701698 (2005)	Acceptable/ Guideline (Y)	142-149	LOAEL = 1000 mg/kg/day, cardiac myofiber degeneration NOAEL = 100 mg/kg/day
870.3465/ 4- week inhalation – Rat	47701699 (2008)	Acceptable/ Guideline (Y)	134-141	NOAEL = 200 mg/ m^3/day (HDT)
Genotoxicity				
870.5100/ Bacterial assay (Ames test)	47701712 (2003)	Acceptable/ Guideline (Y)	149-156	Not mutagenic
870.5300/ *In vitro* mammalian cell gene mutation test: Mouse Lymphoma L5178Y Cells	47889311 (2009)	Acceptable/ Guideline (Y)	431-439	not mutagenic in the presence or absence of S9-activation up to the limit of solubility and cytotoxic effects
870.5375/ Clastogenicity in mammalian cells	47701719 (2003)	Acceptable/ Guideline (Y)	156-167	No evidence of clastogenicity up to its limit of solubility ±S-9.
870.5395/ Micronucleus test in bone marrow	47701720 (2007)	Acceptable/ Guideline (Y)	168-173	No evidence of genotoxicity
870.5550/ In vivo genotoxicity testing – Unscheduled DNA synthesis	The registrant stated that because all other genotoxicity studies are negative, no studies for this data point were performed with regulatory agency concurrence per 28 February 2009 OECD meeting.			
870.5380/ *In vivo* studies in germ cells - Mammalian spermatogonial chromosomal aberration test	Because all other genotoxicity studies are negative, no studies for this data point were performed with regulatory agency concurrence per 28 February 2009 OECD meeting.			
Long-term toxicity and carcinogenicity				
870.4100/ One year chronic (Rat)	47701708 (2008)	Acceptable/ Guideline (Y)	173-186	LOAEL = 1000 ppm, ↓ body weight in males and microscopic findings in the liver (males), heart (females) and urinary bladder (males and females) NOAEL = 50 ppm
870.4300/ Combined chronic and carcinogenicity in rats.	47701709 (2009)	Acceptable/ Guideline (Y)	187-200	LOAEL = 1000 ppm, ↓body weight and food consumption parameters (females) and ↑red-stained urine on cageboards (males). ↑ cardiomyopathy (males and females); urinary bladder mucosal hyperplasia, inflammation, and transitional cell papillomas (males); and sciatic nerve degeneration (females). Oncogenic in male rats at exposures of 1000 ppm and above. NOAEL = 50 ppm or 2.05/2.69 (M/F) mg/kg/day

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
870.4200b/ Carcinogenicity study in mice	47701710 (2009)	Acceptable/ Guideline (Y)	201-218	LOAEL = 228/306 mg/kg/day M/F, degeneration of sciatic and trigeminal nerve axons and their associated myelin sheaths and an ↑ in the incidence (females) and severity (males) of chronic progressive nephropathy. Renal tubular adenomas in males. Oncogenic in male mice. NOAEL = 150 ppm (18.4/25.5mg/kg/day) (M/F)
Reproductive Toxicity				
870.3800/ one-generation reproduction in rats	47701705 (2006)	Acceptable/ Nonguideline	218-243	**Parental toxicity** NOAEL = 250 ppm (16/20 mg/kg/day M/F) LOAEL = 5000 ppm, (339/383 mg/kg/day) ↓bw and gain and food consumption, cardiac myofiber and sciatic nerve lesions, microscopic effects in the heart, liver, muscle, and sciatic nerve of ♂&♀ **Reproductive toxicity** NOAEL = 5000 ppm (339 mg/kg/day) (HDT) **Offspring toxicity** NOAEL = 250 ppm (16/20 mg/kg/day) LOAEL = 5000 ppm (339 mg/kg/day) ↓pup weight during lactation and delayed sexual maturation in both sexes
870.3800/ Multi-generation reproduction in rats	47701706 (2008)	Acceptable/ Guideline (Y)	243-265	**Parental toxicity** NOAEL = 100 ppm (7.2/8.4mg/kg/day) LOAEL = 2000 ppm (144/165mg/kg/day) ↓bw, bwgain and food consumption and ↑ kidney weight, cardiomyopathy and urinary bladder mucosal hyperplasia with inflammation. **Reproductive toxicity** NOAEL = 2000 ppm (135 mg/kg/day) (HDT) **Offspring toxicity** NOAEL = 100 ppm (11 mg/kg/day) LOAEL = 2000 ppm (144/165 mg/kg/day) ↓pup weights and bw gains during lactation
870.3700a/ Developmental toxicity in rats – Range finding	47701701 (2004)	Acceptable/ Nonguideline	266-274	NOAEL for maternal and developmental toxicity = 1000 mg/kg/day (HDT)

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
870.3700a/ Developmental toxicity in rats	47701702 (2007)	Acceptable/ Guideline (Y)	274-282	NOAEL for maternal and developmental toxicity = 1000 mg/kg/day (HDT)
870.3700b/ Developmental toxicity in rabbits – Range finding	47701703 (2004)	Acceptable/ Nonguideline	282-287	NOAEL for maternal and developmental toxicity = 1000 mg/kg/day (HDT)
870.3700b/ Developmental toxicity in rabbits	47701704 (2007)	Acceptable/ Guideline (Y)	287-295	**Maternal toxicity** NOAEL = 1000 mg/kg/day (HDT) **Developmental toxicity** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day reduced fetal weight and increased fetal resorptions
Neurotoxicity				
870.6200a/ Acute neurotoxicity screen in rats	47701721 (2007)	Acceptable/ Guideline (Y)	295-301	NOAEL = 2000 mg/kg/day in males and females (HDT).
870.6200b/ Subchronic neurotoxicity screen in rats	47701722 (2007)	Acceptable/ Guideline (Y)	302-309	**Systemic** NOAEL = 2500 ppm or 161/200 mg/kg/day (M/F), the HDT **Neurotoxicity** NOAEL = 2500 ppm or 161/200 mg/kg/day (M/F), the HDT
870.6300/ DNT rat Range Finding in rats	47701723 (2007)	Acceptable/ Nonguideline	309-318	No effect of maternal treatment, or direct treatment of the offspring on the clinical condition, survival, or macropathology of the dams or the offspring. Lower mean numbers of implantations and litter size at birth at ≥ 600 mg/kg/day
870.6300/ DNT rat	47701724 (2008)	Acceptable/ Guideline (Y)	318-347	**Maternal NOAEL** = 900 mg/kg bw/day (HDT), **Functional development** NOAEL = 900 mkg. **Offspring NOAEL** = 100 mg/kg/day based on ↓ brain weight in ♂and ♀offspring accompanied with a ↓in the thickness of the hippocampus, corpus callosum and cerebellum in PND 21 ♀ offspring at 300 mg/kg/day
Toxicity Study on Metabolites				
870.1100/ Acute oral rat (females) **M-1**	47701678	Acceptable/ Guideline (Y)	Refer to RD	LD_{50} = >2000 mg/kg, Category III
870.1100/ Acute oral rat (females) **M-3**	47701679	Acceptable/ Guideline (Y)	Refer to RD	LD_{50} = >2000 mg/kg, Category III
870.1100/ Acute oral rat (females) **M-25**	47701680	Acceptable/ Guideline (Y)	Refer to RD	LD_{50} = >2000 mg/kg, Category III
870.1100/ Acute oral rat (females) **M-28**	47701755	Acceptable/ Guideline (Y)	Refer to RD	LD_{50} = >2000 mg/kg, Category III
870.1100/ Acute oral	47701681	Acceptable/	Refer	LD_{50} = >2000 mg/kg, Category III

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
rat (females) **I-3**		Guideline (Y)	to RD	
870.1100/ Acute oral rat (females) **I-4**	47701682	Acceptable/ Guideline (Y)	Refer to RD	LD_{50} = >2000 mg/kg, Category III
870.1100/ Acute oral rat (females) **I-5**	47701683	Acceptable/ Guideline (Y)	Refer to RD	LD_{50} = >2000 mg/kg, Category III
870.3050/ 14-Day oral gavage Rat, **KIH-485 M-1**	47701690 (2005)	Acceptable/ Nonguideline	347-350	NOAEL = 1000 mg/kg/day (HDT)
870.3050/ 14-Day oral gavage–Rat **KIH-485 M-3**	47701691 (2008)	Acceptable/ Nonguideline	350-353	NOAEL = 1000 mg/kg/day (HDT)
870.5100/ Bacterial assay (Ames test) **KIH-485 M-1**	47701713 (2005)	Acceptable/ Guideline (Y)	353-358	Not mutagenic (±S9)
870.5100/ Bacterial assay (Ames test) **KIH-485 M-3**	47701714 (2004)	Acceptable/ Guideline (Y)	358-364	Not mutagenic (±S9)
870.5100/ Bacterial assay (Ames test) **KIH-485 M-25**	47701715 (2008)	Acceptable/ Guideline (Y)	364-368	Not mutagenic (±S9)
870.5100/ Bacterial assay (Ames test) **KIH-485 M-28**	47701756 (2009)	Acceptable/ Guideline (Y)	368-373	Not mutagenic (±S9)
870.5100/ Bacterial assay (Ames test) **KIH-485 I-3**	47701716 (2007)	Acceptable/ Guideline (Y)	373-379	Not mutagenic (±S9)
870.5100/ Bacterial assay (Ames test) **KIH-485 I-4**	47701717 (2007)	Acceptable/ Guideline (Y)	380-385	Not mutagenic (±S9)
870.5100/ Bacterial assay (Ames test) **KIH-485 I-5**	47701718 (2007)	Acceptable/ Guideline (Y)	386-391	Not mutagenic (±S9)
Non-guideline/DEREK Evaluation of KIH-485 Metabolites M-1, M-3, M-9, M-25 and M-29	47701757 (2009)	NA	392-392	Neither pyroxasulfone nor the five metabolites evaluated fired any structural alerts for toxicity.
Other Special Studies				
870.7485/ Metabolism in Dogs	47701726 (2005)	Acceptable/ Nonguideline	393-401	Metabolism, absorption, pharmacokinetics, excretion – metabolic path
870.7485/ Metabolism in Mice	47701730 (2007)	Acceptable/ Nonguideline	401-408	Metabolism, absorption, pharmacokinetics, excretion – metabolic path, whole body autoradiography
870.7800/Immunotoxicity-Rats	47701731 (2006)	Acceptable/ Guideline	408-415	Not immunotoxic at 7500 ppm (HDT)
870.7800/Immunotoxicity-Mice	47701732 (2008)	Acceptable/ Guideline	415-421	Not immunotoxic at 4000 ppm (HDT)
Non-guideline/ Lacteal secretion in the rat	47701727 (2006)	Acceptable/ Nonguideline (N)	421-425	Concentrations of radioactivity in milk and plasma and their half lives were investigated following single oral

File 1				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
				dosing.
Non-guideline/ Transfer of radioactivity into stomach contents of rat offspring	4770125(2006)	Acceptable/ Nonguideline (N)	425-430	Transfer of radioactivity into stomach contents of rat offspring following repeated oral administration to the dam was investigated
870.7600/ Dermal absorption (*in vivo*)	NA	NA	393	Not required for US or Australia and waived for Canada per 28 February 2009 OECD meeting
Correspondence				
870.3465/90-Day Inhalation	NA	NA	447	Waived per letter dated April 16 2009
870.3250/90-Day Dermal	NA	NA	449	Waived per letter dated April 16 2009
870.4200b/ Carcinogenicity study in mice	NA	NA	450	Dose Selection letter July 21, 2006

[a]Y= The study satisfies the guideline requirement. N= Does not satisfy the guideline requirement. O= satisfies the guideline requirement when combined with other studies.

File 2				
Study Type	**MRID (year)**	**Classification (Y/N/O)[a]**	**Pages**	**Comments**
Non-guideline/ A Toxicological Mechanism Study: Effects on motor systems in mice after 14-day dietary exposure using a glutathione depletion animal model	48046901 (2009)	Acceptable/ Nonguideline (N)	3-10	Mice fed 20000 ppm pyroxasulfone showed wasting of muscle at termination, reduced body weight and food consumption. With concomitant gross pathological and histopathological changes. Pyroxasulfone appeared to augment the depletion of the intracellular GSH in muscular tissues. However, there was no control group treated with pyroxasulfone alone without the BSO. Additionally no attempts were made to measure biochemically glutathione in the muscular tissues.
Non-guideline/ Heart histopathology for a toxicological mechanism study of Pyroxasulfone	48046902 (2010)	Acceptable/ Nonguideline (N)	11-12	Pyroxasulfone induced very mild myocardial toxicity in mice at the dietary level of 20000 ppm under the GSH depleted conditions of the study.
Non-guideline/ Investigation for Cell Proliferation Activity and Oxidative Stress in Rat Urinary Bladder After 14 days dietary exposure.	48046903 (2009)	Acceptable/ Nonguideline (N)	13-19	Male CD rats treated with 2000 and 20000 ppm KIH-485 in the diet for 14 days showed increased cell proliferation associated with hyperplasia in the urinary bladder epithelium as measured by the Ki-67 labelling. There were no changes in the malonaldehyde (MDA) content of the bladder
Non-guideline/ Investigation for Cell Proliferation Activity and	48046904 (2009)	Acceptable/ Nonguideline (N)	19-25	Male CD1 mice treated with 2000 or 15000 ppm KIH-485 in the diet for 14 days did not exhibit cell proliferation activity or oxidative

File 2

Study Type	MRID (year)	Classification (Y/N/O)[a]	Pages	Comments
Oxidative Stress in Mouse Kidneys After Dietary Exposure for 14 Days				stress in the kidney.
Non-guideline/ Electron Microscopic Examination of Rat Urinary Bladder Treated with Pyroxasulfone (KIH-485) for 14 Days	48046905 (2010)	Acceptable/ Nonguideline (N)	26-30	Doses of 2000 and 20000 ppm of KIH-485 (pyroxasulfone) induced morphological changes in the surface of the bladder epithelium but does not appear to be due to microcrystal in rat urinary bladder under the conditions of this study.
Non-guideline/ Rat In Vivo Comet Test.	48033306 (2010)	Acceptable/ Nonguideline (N)	31-37	Pyroxasulfone has caused an increase in the tail intensity in the bladder and liver cells of male Sprague Dawley rats, when administered orally by gavage at 1000 mg/kg and above (bladder) and at 2000 mg/kg (liver) in the *in vivo* test system.
Non-guideline/ Mouse In Vivo Comet Test.	48033307 (2010)	Acceptable/ Nonguideline (N)	37-44	In kidney cells, pyroxasulfone administration causes increase in tail intensity only at 2000 mg/kg bw/d in mice.
Non-guideline/Mode of Action Report	47948801 (2010)	NA	44-45	The proposed mode of action for renal tubular adenoma (male mice) and urinary bladder transitional cell papilloma (male rats) following treatment with pyroxasulfone was not supported by experimental evidence.

[a]Y= The study satisfies the guideline requirement. N= Does not satisfy the guideline requirement. O= satisfies the guideline requirement when combined with other studies.